

REMARKS

I. Status of the Claims

Claims 1, 29-37 and 39-74 are pending in the application. The Office Action stated that claims 1, 29-44, 49 and 50 have been rejected. Claim 38 has been previously cancelled, so claims 1, 29-37 and 39-74 are properly pending in the application. Claims 1, 29, 32, 33, 36, 37, 39-44 and 49 have been amended. Claims 45-48 and 51-74 have been withdrawn. Claim amendments are for the purposes of improved clarity or consistency of claim language unless otherwise noted. No claim amendment should be construed as an acquiescence in any ground of rejection. Claims have been amended without prejudice to pursuing the cancelled subject matter in a continuing application. No new matter has been added by this amendment. Support for the amendment can be found throughout the specification and claims as filed and, for example, on page 16, lines 22-24 of the specification.

II. Election/Restriction

Applicants' election of Group I, claims 1, 29-37 and 39-74, with traverse, has been acknowledged. Further, applicants' election, with traverse, of a species of claim 34 wherein said 2' substituent is 2'-deoxyribonucleotide for the first portion has been acknowledged. Applicants' election, with traverse, of a species wherein said 2' substituent is 2'-O-alkyl for the further portion has been acknowledged.

Where applicants have elected claims directed to a product and the product claims are subsequently found allowable, applicants request that the withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claims will be rejoined in accordance with the provisions of MPEP § 821.04.

III. Information Disclosure Statement

A supplemental information disclosure statement is enclosed for U.S. Patent No. 5,898,031 and EP 0788366 B1.

IV. Double Patenting

Claims 1, 29-32, 49 and 50 have been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claim 6 of U.S. Patent No. 6,617,442. In the event that claims 1, 29-32, 49 and 50 are otherwise found to be in condition for allowance in their current form, applicants will file a terminal disclaimer.

V. Claim Objection

Claim 36 has been amended to correct an informality by deleting the word “from”. Claim 36 has been amended solely to clarify and not limit the claim.

VI. The Claims are Definite under 35 U.S.C. § 112, second paragraph

Claims 37 and 39-44 have been rejected under 35 U.S.C. § 112, second paragraph as allegedly being indefinite in reciting the limitation “said nucleotides of said further portion.”

Claims 37 and 39-44 have been amended to include the phrase “said further portion comprises a plurality of nucleotides and wherein...” thus obviating the rejection. Claims 37 and 39-44 have been amended solely to clarify and not limit the claim.

VII. The Claims are Novel under 35 U.S.C. § 102 (b)

Claims 1, 29-32, 34-44, 49, and 50 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Agrawal et al. (WO 94/01550). Applicants traverse the rejection.

Claims 1 and 29, as amended, are directed to a mixed sequence oligonucleotide comprising at least 12 nucleotides in length and having a 3' end and a 5' end and divided into a first portion and a further portion wherein, in part, said first portion comprises at least 6 contiguous nucleotides and is positioned in said oligonucleotide such that at least one of said at least 6 contiguous nucleotides is 8 to 12 nucleotides from the 3' end of said oligonucleotide. Claim 49, as amended, is directed to a chimeric oligonucleotide comprising 8 to 25 nucleotides wherein, in part, said portion supporting said cleavage is at least 6 contiguous nucleotides in length and is positioned in said oligonucleotide such that at least one of said at least 6 contiguous nucleotides is positioned 8 to 12 nucleotides from the 3' end of said oligonucleotide. Claim 32 is directed to a mixed sequence oligonucleotide wherein, in

part, "each of said nucleotides of said first portion... are joined together in a continuous sequence." The Agrawal reference does not anticipate the claimed invention since Agrawal does not teach an embodiment that falls within the scope of the present claimed invention.

The Agrawal reference does not anticipate the claimed invention since the reference does not teach a mixed sequence oligonucleotide wherein, in part, said first portion comprises nucleotides that support cleavage of a complementary target RNA by human RNase H1 polypeptide and wherein said first portion comprises at least 6 contiguous nucleotides and is positioned in said oligonucleotide such that at least one of said at least 6 contiguous nucleotides is 8 to 12 nucleotides from the 3' end of said oligonucleotide. The Agrawal reference does not teach any compound that falls within the scope of the present claimed invention. The examiner pointed to Compound D in Figure 5. Compound D does not have a sequence portion that is at least 6 contiguous nucleotides positioned 8 to 12 nucleotides from the 3' end of the oligonucleotide. In particular, Compound D does not have a first sequence portion that is at least 6 contiguous nucleotides. Furthermore, the examiner has not correctly interpreted the nucleotide positioning in compound D in Fig. 5 of Agrawal. The examiner asserted that the final T in the loop, which is complementary to the first 5' G of the gag RNA, is 8 nucleotides from the 3' end. In fact, this nucleotide is 9 nucleotides from the 3' end, based on the numbering system where the 3'-most nucleotide, G, is the first nucleotide from the 3' end. This numbering is accepted in the art, and an example is described in the instant application, for example, in the paragraph on page 46, line 13-34 and in Figure 3. None of the compounds described in Figure 5 or elsewhere in the Agrawal reference have a first portion nucleotide sequence that supports cleavage by RNase H and that is at least 6 contiguous nucleotides positioned 8 to 12 nucleotides from the 3' end of the oligonucleotide. Therefore, the Agrawal reference does not anticipate the present claimed invention. Furthermore, the oligonucleotides including modified nucleic acid bases and/or sugars of the Agrawal reference do not anticipate claims 1, 29-32, 34-44, 49, and 50, as amended in the present claimed invention. Accordingly for these reasons, applicants respectfully requests that the examiner withdraws the instant rejection of claims 1, 29-32, 34-44, 49, and 50 under 35 U.S.C. § 102(b).

VII. The Claims are Not Obvious under 35 U.S.C. § 103 (a)

Claims 1, 29-44, 49, and 50 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Agrawal et al. (WO 94/01550), Beigelman et al. (1995) *Nucleic Acids Res.* **23**: 4434-4442, and Colman (1990) *J. Cell Science* **97**: 399-409. Applicants traverse the rejection of claims 1, 29-37, 39-44, 49, and 50. Claim 38 has been cancelled.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation to modify the reference or to combine the reference teachings so as to arrive at the claimed invention and there must be a reasonable expectation of success for achieving the claimed invention as a whole. See *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Here, a proper *prima facie* case of obviousness has not been set forth.

Claims 1, 29, 32, and 33 as amended, are directed to an oligonucleotide comprising at least 12 nucleotides in length and having a 3' end and a 5' end and divided into a first portion and a further portion wherein, in part, said first portion comprises at least 6 contiguous nucleotides and is positioned in said oligonucleotide such that at least one of said at least 6 contiguous nucleotides is 8 to 12 nucleotides from the 3' end of said oligonucleotide. The Agrawal reference in view of the Beigelman reference and the Colman reference do not teach or suggest all elements of the claimed invention. As discussed above, the Agrawal reference does not teach or suggest the claimed invention since Agrawal does not teach an oligonucleotide comprising, in part, a first portion wherein at least one of said 6 contiguous nucleotides is 8 to 12 nucleotides from the 3' end of said oligonucleotide. Furthermore, the oligonucleotides including modified nucleic acid bases and/or sugars of the Agrawal reference do not fall within the scope of the present claimed invention.

With regard to claim 33, the claimed mixed sequence oligonucleotide provides that each of the nucleotides of the first portion is, independently, a modified ribonucleotide. This language requires that every nucleotide in the first portion, which is 6 or more contiguous nucleotides in length, contain one of the 2' modifications listed in claim 33. The Agrawal reference in view of the Beigelman reference and the Coleman reference do not teach incorporating 2' modifications to an oligonucleotide first portion comprising at least 6 contiguous nucleotides, and in fact, teach away from making such modifications. The Beigelman reference teaches modifying no more than two nucleotides of a ribozymes. See Beigelman et al., for example, Table 1. The Beigelman reference teaches that using extensive

2' sugar modifications can interfere with catalytic activity and that maintaining an optimal balance between higher cleavage activity and nuclease resistance requires selective modification at positions U4 and U7. See Beigelman et al., for example, page 4434, column 2. Furthermore, the Beigelman reference teaches that certain modifications of the ribonucleotide resulted in ribozymes with reduced activity, and that modification at two positions (U4 and U7) gave a more pronounced negative effect. See, for example, page 4438, Table 1. The Coleman reference does not cure the deficiencies of the Agrawal reference and the Beigelman reference. The Coleman reference, alone or in combination with the other references, does not teach or suggest the claimed oligonucleotide wherein each of the nucleotides in the first portion is independently, a modified ribonucleotide. The Agrawal reference in view of the Beigelman reference and the Coleman reference do not teach or suggest the claimed invention. Thus, at the time of the instant claimed invention, the Agrawal reference, in view of the Beigelman and Coleman references, would not provide a motivation to one of skill in the art to make applicants' claimed invention nor provide a reasonable expectation of success in making the claimed oligonucleotides. Applicants therefore request that the rejection of claim 1, 29-37, 39-44, 49, and 50 under 35 U.S.C. § 103(a) be withdrawn.

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VIII. Conclusion

In view of the foregoing, applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

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/Phillip A. Singer/
Phillip A. Singer
Registration No. 40,176

Woodcock Washburn LLP
Cira Centre
2929 Arch Street, 12th Floor
Philadelphia, PA 19104-2891
Telephone: (215) 568-3100
Facsimile: (215) 568-3439